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14. ABSTRACT

Background and Significance. Pain is common in multiple sclerosis (MS) but is currently under-recognized and under-treated due in part to the absence of adequate metrics. The specific aims of this study are: (1) To create an fMRI pain metric designed specifically for individuals with MS that uses the minimum level of somatosensory stimulation necessary to elicit increased activation of thalamus, cingulate, insula, and sensorimotor cortex ("augmented central pain processing") in MS patients compared to controls, and (2) To determine the relationship between augmented central pain processing, as measured using fMRI, to self- and clinician-administered pain measures and to thalamic volume loss in the patient group. Participants will include patients with relapsing-remitting MS, diagnosed according to standard criteria at our MS Center, and demographically matched healthy controls. To date, we have developed, implemented, and tested the fMRI stimulation paradigm for this metric, and have started screening and scanning participants. We were granted an Extension Without Funds of one year to complete the research. Results will be available when we have accrued the complete participant sample (in Months 10-12 of the extension period).

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Introduction

The subject of this study is pain in multiple sclerosis (MS). One-half to two-thirds of individuals with multiple sclerosis (MS) experience pain, often characterized by chronic painful sensations of the extremities and face, including burning, itching, and other sensations. However, pain is currently under-recognized and under-treated in MS due in part to the absence of adequate metrics. Pain assessment in MS has so far relied on subjective self-report and clinician-administered measures. The rationale for this study is based on the fact that functional magnetic resonance imaging (fMRI) of pain circuitry offers a complementary, more objective approach for pain assessment, and provides insight into central pain mechanisms. Furthermore, fMRI studies in other pain conditions show increased activity of pain circuitry, including thalamus, cingulate, insula, and sensorimotor cortex, relative to controls (termed "augmented central pain processing"). The purpose of this study is to develop and test an fMRI probe as a valid, reproducible, and minimally invasive pain measure targeted for patients with MS. The scope of the research includes (a) developing the fMRI probe and (b) testing it in patents with MS (N=15) and demographically matched healthy controls (N=15). Participants will undergo fMRI during minimal pain stimulation, and we will test the hypothesis that patients show augmented central pain processing (i.e., greater activity of pain circuitry) relative to controls. We will also assess how brain activation patterns during pain stimulation relate to self-rated pain and volume of the thalamus in the patient group.

Body

In the first 12 months of the study, we had originally planned in our statement of work to complete enrollment (Task 1) in months 1-9; testing and scanning (Task 2) in months 1-10; and data analysis and reporting (Task 3) in months 11-12. However, there was an unavoidable delay in implementing our MRI-compatible pain stimulation paradigm. We had to abandon our intended air pressure-based paradigm because it could not be effectively implemented within our imaging center and, after evaluating stimulation paradigms published by several groups in the US and Australia, we identified a new hydraulic-based stimulation paradigm which we then successfully implemented. This delayed the project by months. Because of the delay in ascertaining what pain stimulation paradigm we would employ, our IRB and DOD Human Subjects approvals were also unavoidably delayed, but those were approved as of July 2011 (and remain current). By the end of the first 12 months of the study, we had implemented and performed pretesting on our pain stimulation paradigm, and we had our first three participants scheduled.

We submitted and had approved a request for an extension without funds (EWOF) for an additional 12-month period (Sept. 2011-Aug. 2012) during which our planned statement of work includes: enrollment (Task 1) in months 1-9; testing and scanning (Task 2) in months 1-10; and data analysis and reporting (Task 3) in months 11-12.

We have now enrolled, tested and scanned one patient and three healthy controls (Tasks 1 and 2). Procedures include threshold testing, completion of subjective measures, and scan acquisition:

Threshold testing: Graded blunt pressure stimulation thresholds are established for each individual prior to scanning using standard psychophysical procedures. As in prior fMRI pain research[1, 2], mechanical pressure is applied to the thumbnail of the right hand for 5 second periods interspersed with 20 seconds of no pressure to prevent sensitization of the site of stimulation. Stimulation of the thumbnail has been demonstrated to lead to augmented central pain processing on fMRI even when the site(s) of the individual's pain are in other bodily location(s). Using a repeated ascending staircase method, thresholds are obtained for "mild" pain ratings on two separate runs using a combined numerical/ verbal scale of 0 to 20. Participants provide ratings immediately after each stimulus, and the number of trials required to establish each threshold is recorded for assessment of the consistency of ratings over the course of the procedure.

Subjective Measures. Participants complete our verbally anchored 10-point global pain severity scale; the McGill Pain Questionnaire[3] (a well-validated pain questionnaire which includes a bodily location chart, 20 pain adjective categories, and questions regarding pain intensity and temporal characteristics), the Pain Effects Scale[4] (which assesses the degree to which pain interferes with daily activities); and mood screening tests.

Scan Acquisition and Processing: Echo Planar fMRI: Our fMRI pain task is administered to each participant using MR-compatible equipment on our research-dedicated Philips Achieva 3T scanner (TR: 2000 ms, TE: 35ms, flip angle: 70, FOV: 240mm, slice thickness: 3.75mm, NEX: 1, yielding 42 contiguous axial slices in a 64 x 64 matrix with isotropic resolution of 3.75 mm^3). Each run lasts approximately six minutes and includes alternating periods of 5 seconds of stimulation and 20 seconds of rest (no pressure). Degree of pressure stimulation is based on the individual's pre-scanning threshold testing. fMRI preprocessing is carried out using MATLAB7.11 (The MathWorks, Inc.) and Statistical Parametric Mapping (SPM8), and includes: data reconstruction; realignment,

unwarping and calculation of motion parameters; rigid body registration to standard space; and spatial smoothing (FWHM=4 mm). Structural MRI scanning includes a sagittal survey 3-plane localizer, an M2D/TFE T1-weighted survey with 10mm slice thickness; a sagittal T1-weighted MP-RAGE 3D anatomical volume (170 contiguous 1.2 mm sagittal slices, TR: 6.8ms, TE: 3.2ms, TI: 852.9ms, TFE prepulse delay: shortest, flip angle: 8 deg, NEX: 1, BW/Pixel: 241, FOV: 256mm, matrix 256x256, 1.0 mm^2 in-plane resolution); an axial fluid-attenuated inversion recovery (FLAIR) scan (slice thickness: 3mm, TR: 11000, TE: 125, TI: 2800, TFE: 27, flip angle: 120, NEX: 1, BW/Pixel: 223.9/1.940, FOV: 240 mm). The high-resolution T1 volumes and FLAIR scans are acquired for quantification of whole brain, thalamic, and lesion volume using the fMRIB Software Library (FSL) and our in-house software[5] for the purpose of characterizing the sample and for use in the statistical analyses.

In addition to the enrolled participants, we have prescreened numerous additional patients, however, upon contacting patients for the second stage of screening, which includes an in-depth telephone interview, we are finding they often meet exclusion criteria. Recruitment of healthy controls is yoked in time to patient recruitment (in order to avoid temporal effects, such as scanner drift), and so once we reduce the bottleneck on patient recruitment, we can proceed as planned with control recruitment. We are therefore about to submit a request to revise the exclusion criteria to enable us to recruit the required number of patients and to make the sample more representative of the MS population.

Thus, we remain in progress for Tasks 1 and 2 in our EWOF period at this time. We will be able to report on the findings of this study (Task 3) once we have tested the participants and analyzed the data.

Key Research Accomplishments

- We have developed and implemented a minimally invasive pain fMRI probe tailored for patients with MS, and will continue testing it during the EWOF period. We will have additional key research accomplishments to report once we accrue and analyze the data (Task 3).

Reportable Outcomes

- We have applied for an NIH R01 to continue work on imaging the neural basis of pain in MS. We will have additional reportable outcomes (manuscript, abstract, and/or presentations) to report once we accrue and analyze the data (Task 3).

Conclusion

We have developed and successfully implemented a pain fMRI procedure tailored for patients with MS, using minimally invasive pain stimulation. Our progress was initially delayed due to needing to change from our intended pneumatic system to a hydraulic-based pain fMRI probe, but we received an EWOF to continue the research and have now tested the approach in 1 patient and 3 healthy controls. Thus, we remain in progress on Tasks 1 and 2. We have found that we will need to request a change in the exclusion criteria in order to recruit sufficient numbers of patients and make the sample representative of the MS population, and will be submitting this request shortly. Control recruitment is yoked in time to patient recruitment, so once we remove the bottleneck on patient recruitment, we will be able to proceed with control recruitment as well. We will be able to report the findings of this study once we have accrued and analyzed the data (Task 3). Ultimately, this line of research will (a) contribute to improved scientific understanding of the role of CNS changes in pain in MS, and (b) make available a pain fMRI metric that can be used in future research on pain in MS (e.g., to test effects of pain treatments on activity of pain circuitry in the brain) and that can be further developed for eventual use in clinical scanning.

References – (This is literature cited in support of the above rationale and procedures for this study. These are not references emanating from this study.)

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Appendices - None